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In my letter to you of January 27, 2000, I provided comments on matters pertaining to malathion being considered by HED's Cancer Assessment Review Committee (CARC) as agreed to at the January 13 meeting. In the present letter I shall attempt to present a similar assessment of non-cancer issues reviewed by HED's Hazard Identification Assessment Review Committee (HIARC), also as agreed to at the January 13 meeting. I have attempted to provide a list of "Substance" and a list of "Process". Each topic in the "Substance" list is simply framed, while the supporting documentation is more fully set forth in the memoranda or publications cited in each case. The background discussion may be lengthy. Persons interested in evaluating these subjects must examine the cited documents for factual information and the rationale

Electronic "icons" for the various documents as referred to below in bold type are briefly identified in the Attachments.

I - "Substance":

1) *Food Quality Protection Act (FQPA) 10X Safety Factor for Protection of Infants and Children:* **057701ha.002:** pp. 6-8; **Att 1; Att 2:** pp. 48, 50, 57- 64; **Att 6:** pp. 109-110; **Att 8**; **Att 11**; **Att 12:** pp. 124-126*;* **Att 13**; **Att 14**; **Att 15**; **Att 16**; **Att 17**; **Att 18:** pp. 148-155.

The HIARC's decision to delete the FQPA imposed 10-fold safety factor for the protection of infants and children is unsupported by the data base. Reduction or removal of the Congressionally imposed 10X safety factor is conditioned upon: 1) a *reliable* data base, 2) a *complete* data base and 3) evidence that *young/developing individuals are no more susceptible than adults* to the toxicologic effects of the agent in question. ***All*** of these conditions must be met. Yet, in my witness, ***none*** of the conditions are met for malathion. The rationale for removal of the factor as presented in the December 17, 1997 HIARC report (**Att 2**) is inadequate, and there is little evidence the subsequent August 6, 1998 report of the FQPA Safety Factor Committee (t-drive available), also recommending the safety factor's removal, contributed any more definitive evidence. When questioned as to the adequacy of the data base to remove the safety factor, the External Peer Review did not support the factor's removal, based upon the inadequate reliability of the data base to address the susceptibility issue; and the incompleteness of the data base, as evidenced by the need for cholinesterase data in exposed young versus adult animals and additional behavioral effects testing. The External Peer Review Panel characterized a variety of deficiencies and needed studies as data gaps. (**Att 16**) Now whether these deficiencies are data gaps in the strict sense of being unsatisfied end points in Guideline studies (as I believe some in fact are), or inadequacies in the overall assessment of malathion to address health effects concerns, is probably one more of semantics than substance with respect to the intent of Congress to protect infants and children. If there is serious doubt as to the intent of Congress, then ask the

Congressional author(s) of the FQPA.

To the extent the data base is not *complete*, it is not *reliable* and vice versa. Additional Guideline data gaps do exist (subchronic inhalation, subchronic cholinesterase in the dog), though these tests do not directly address the question of *susceptibility*, they do establish the absence of a complete data base in terms of Guideline requirements. In my opinion, as supported by that of the External Peer Review, the data illustrate a need for further behavioral effects testing, a requirement that *might* be satisfied by the Guideline Developmental Neurotoxicity Study recently being required by OPP for all organophosphates. In the case of malathion, to the extent that a need for such testing has been identified based upon published works which indicate behavioral effects and/or effects on learning and memory at low doses, the requirement for additional behavioral effects testing is therefore more than generic, and thus in effect constitutes another data gap that should be satisfied *prior* to removal of the 10X factor. The Developmental Neurotoxicity does pertain to the *susceptibility* issue.

As to the question of differential *susceptibility* revealed in the malathion Guideline reproduction study, I do not accept HIARC's rationale for discounting the actual evidence of enhanced susceptibility of the offspring. I believe my views are well presented in the background materials cited. Furthermore, I have recommended an *external* re-review of the reproduction study, focused on the differential susceptibility aspect.

In addition to evidence of increased susceptibility of offspring in the Guideline reproduction study, evidence has been cited of increased susceptibility of the young exposed to malathion [**Atts 17** and **18** (p. 154)] which was not identified in the December 17, 1997 HIARC report. This additional information was also not acknowledged by the committee in its final December 22, 1998 report.

Parenthetically, though not previously mentioned in the HIARC or FQPA Safety Factor Committee's consideration of malathion, the National Research Council's (1993): "Pesticides in the Diets of Infants and Children" (the report which spawned FQPA) indicates that: "There is speculation that neonates and infants may be more susceptible to chemically induced neurotoxicity, in part because of the immaturity of their blood-brain barrier. Watanabe et al (1990) point out that the central nervous system in developing individuals is potentially vulnerable to chemicals for a protracted period because the central nervous system requires longer than most other organ systems for cellular differentiation, growth, and functional organization. Therefore, any increase in accessibility to cytotoxic agents because of delayed maturation of the blood-brain barrier could have serious consequences." (p. 89) Currently, OPP gathers no data on the relative accessability of cholinesterase inhibitors to the CNS of adult versus young animals. Since cholinesterase inhibition is a most fundamental end point for an agent designed to inhibit that enzyme, differential inhibition in adult versus developing individuals may be expected to be a most sensitive indicator of differential susceptibility. As said previously, and as supported by the External Peer Review, the data base lacks *reliability* to address the susceptibility issue absent cholinesterase data, particularly in developmental toxicity and reproduction studies.

2) *Hazard Identification/Acute Oral (One-Day):* **057701ha.002:** pp. 4-5; **Att** 1; Att **2:** pp. 50-52; **Att 6:** pp. 108-109; **Att 12:** p. 124

HIARC has set the Acute RfD at 0.05 mg/kg/day despite the fact that in addition to myself, all members of the External Peer Review Panel say it is not supportable, principally due to the absence of cholinesterase activity assessments in the critical study (developmental toxicity study), where body weight change, a relatively insensitive parameter, serves as the basis of the end point. The HIARC decision *assumes* in the absence of actual data that cholinesterase inhibition, or another more sensitive or serious parameter, e.g. behavioral effects, would not be affected after a single dose of this magnitude. I do not accept that a developmental toxicity study provides sufficiently rigorous data to serve as the basis for defining this critical end point.

3) *Hazard Identification/Chronic Dietary (RfD):* **057701ha.002:** pp. 8-9; **Att** 1; Att **2:** 52-53, 74-88; **Att 3**; **Att 4:** pp. 103-104; **Att 5**; **Att 6:** p. 110; **Att 12:** pp. 127-129; **Att 18:** pp. 149-150.

The HIARC established the Chronic RfD based upon cholinesterase inhibition as derived from the combined chronic toxicity/carcinogenicity study in the rat. This decision was rendered though two members of the External Peer Review Panel, in addition to myself, affirmed retention of the human study as the basis for the RfD, while the third panel member, though supporting the rat study, advocated an additional 3-fold uncertainty factor be applied to address study deficiencies in the rat [“...., principally because the critical effect was not monitored in the 2 generation reproductive study in a potentially sensitive subgroup [i.e., *young rats* (emphasis added)].” (Dourson, p. 30) Dr. Dourson also advocated an additional 3-fold safety factor be applied to the human study derived RfD, should it be retained: “The use of the human data has the obvious advantage of relevance. However, it does not test females, so the NOEL/LOEL range could potentially be lower. The use of the data base factor of 3-fold would also lower the RfD.” (p. 30) So the HIARC has disregarded the recommendations of the entire External Review Panel; as well as my recommendation, which was to retain the human study (with an added uncertainty factor to compensate the absence of cholinesterase data in women), while conducting a more definitive assessment of cholinesterase inhibition in the rat. However, I am also enamored of Dr. Dourson’s expressed concerns over the absence of cholinesterase data in young rats, which applies, I might add, to the human data as well, as being consonant with FQPA concerns. In retaining its decision, the HIARC has not specifically addressed the rationale of Panel members nor myself. The Panel had much to say, the content of which may be found in their appended responses (**Att 1**) and is summarized in my July 21, 1998 memorandum (**Att 12**)

4) *Subchronic Inhalation Study:***057701ha.002:** pp. 10-11; **Att 2:** pp. 56-58; **Att 6:** pp. 111-112; **Att 9**; **Att 10**; **Att 12:** pp. 129-131; **Att 18**, pp. 150-152.

At the HIARC meeting of November 6, 1997, the Committee imposed an additional UF of 3 for the intermediate and long term, but not the short term exposure risk assessments. Initially, I

disagreed with the use of only a 3-fold UF. Subsequent to receipt of the two-week dose range-finding inhalation study and results of the External Peer Review, the HIARC revised the UF to 10, and directed it be applied to all three time frame risk assessments. The application to short term exposure risk assessments was the result of the finding of nasal histopathology after only two weeks exposure as revealed in the range-finding study. I am concerned as to just how soon following malathion exposure by the inhalation route, effects on the nasal mucosa would be seen, and that HIARC affirm the importance of determining this endpoint in the new inhalation study being required by HIARC. *The final HIARC report leaves unaddressed the question of whether a carcinogenicity study by the inhalation route should be performed.* (p. 11) In addressing the comments of the External Peer Review Panel, I do not agree with the presentation as set forth in the final HIARC report. My assessment of the responses of the Panel, as presented in my November 5, 1998 comments on the October 27, 1998 draft HIARC report (**Att 18**, p. 150) should have been addressed in the final HIARC report. (pp. 10-11)

5) *Acute Neurotoxicity Study (Retinal Histopathology):* **057701ha.002:** pp. 12-13; **Att 1**; **Att 2:** p. 61, 68-72, ; **Att 4**; **Att 7**; **Att 12:** pp. 131-132.

The final HIARC report rejected my recommendation for the submission of a selected few retinal slides for further histopathology assessment, as well as my recommendation that retinal slides from lower dose group animals be examined. These questions were among those submitted to the External Peer Review Panel. The Panel members were provided HED's December 7, 1997 *ad hoc* report along with the complete set of DERs for consideration. Their decision was that the slides bearing retinal rosette should be submitted for independent diagnosis/characterization, and that the lower dose group (s) in the study should be examined histopathologically. *Since receiving the External Peer Review results, the HIARC has offered no new reasons to rebuff the external toxicologists recommendations.*

6) *Subchronic Neurotoxicity Study (Recommendation for Additional Behavioral Effects Testing):* **057701ha.002:** pp. 13-14; **Att** 1; **Att 2:** pp. 61, 63-65, 71-72; **Att 4:** pp. 104-105; **Att 6:** pp. 108-109; **Att 12:** pp. 132-134; **Ehrich**.

The contrast between the NOEL of 1575 mg/kg/day on neurotoxicity end points (FOB; motor activity) in the Guideline Subchronic Neurotoxicity Study in the rat, and that of a *LOEL* of 38 mg/kg/day on a different set of neurotoxicity parameters (learning/memory; EEG; EMG) in a published work, Desi et al (1976), has been noted. My recommendation has been that this published work be considered of sufficient merit and concern, because of the low doses involved, to trigger a study of malathion on behavioral, learning/memory or cognitive end points not evaluated in the existing Guideline study. I have noted that cholinesterase inhibition reported in Desi et al is consistent with that in the Guideline study, which serves to enhance the credibility of both studies. In support of Desi et al, I have also cited Kurtz (1977), in which malathion was shown to elicit avoidance behavior in rats following single doses as low as 50 mg/kg (but not 25 mg/kg) and above as administered intraperitoneally. HIARC, on the other hand, discounted these published works as being of sufficient merit even to *elicit further testing*. According to my

interpretation, two members of the External Peer Review Panel support a requirement for additional neurotoxicity behavioral effects testing, though one of these Panelists, Dr. Hartung, in reference to Desi et al, questions the reliability of "Russian neurophysiology". I should note in response that the article in question appeared in a recognized, peer reviewed, Western journal. Dr. Decker heartily supported the testing. The third Panelist, Dr. Dourson, says: "I do not believe that it does. The LOEL of 38 mg/kg-day for both cholinesterase depression and possible learning effects is not inconsistent with the cholinesterase NOEL of 4 mg/kg-day from the 2 year rat bioassay." (**Att 1**, p. 35). Dr. Dourson seems to be saying the finding is not surprising or unexpected, results in the Guideline testing not withstanding.

A journal publication [(Ehrich et al (1993)], not identified in HIARC's 1997 report: "Information from the Open Literature" (p. 63), nor subsequently by the FQPA Safety Factor Committee, reported that malathion at all *single* dose levels administered, the lowest being 600 mg/kg/day, yielded positive responses on EPA's FOB parameters before or by day 21 post dosing. This study in conjunction with other published works should be reviewed by HIARC and the FQPA Safety Factor Committee in its consideration of the *reliability* of the data base, and more specifically with respect to the recommendation for the Developmental Neurotoxicity Study, or other cognitive effects testing for malathion.

7) *Cholinesterase Inhibition - Enhanced Sensitivity of Females:* **057701ha.002:** pp. 14-15; **Att 2:** 69-70; **Att 4**; **Att 5**; **Att 10**; Att **12:** p. 134-135; **Att 18:** pp. 153, 156. Information illustrating the gender specific disparity was presented to HIARC at the November 6, 1997 meeting, where a decision was rendered for the matter to be considered by an *ad hoc* group. The report of that *ad hoc* group says: "Regarding the possibly greater sensitivity of females (as compared to males) to the cholinesterase inhibiting effects of malathion, the results of cholinesterase determinations in *numerous studies* (emphasis added) on malathion were discussed and it was agreed that females do indeed appear to be more sensitive than males." (**Att 2**) Those "numerous" studies that were before the committee are part of the overall background materials that were available to the HIARC and the External Peer Review Panel, though are not included in this package; one exception being **Att 10**. Nevertheless, the *ad hoc* committee did conclude females to be more sensitive, but felt the difference was too small to merit imposition of an additional modifying factor. I disagreed with that decision concerning the magnitude of the effect as being too small to merit an uncertainty factor. Later, I concluded that a consensus exists among the External Peer Review Panel that females are more sensitive. Furthermore, there was a consensus (unanimous if the human study on male prison volunteers is retained for the RfD) among the Panelists that additional testing be performed in animal models to further quantitate the gender specific disparity. (**Att 12**) Yet, in spite of these considerations, it was my observation at the final HIARC meetings of August 1998, that the "Expert" chosen to address this issue merely proclaimed there was no gender specific disparity, while the final HIARC report: 1) proclaims things not consistent with my recollections; 2) resorts essentially to the language previously employed by the *ad hoc* committee; and 3) says that additional testing is not necessary. The External Peer Review has again been discounted by HIARC. The bottom line is summarized as

follows: I am convinced females are sufficiently more sensitive to merit an additional modifying factor for the human (male only) study derived RfD, should that be retained. Furthermore there is both reason and precedent to employ a modifying factor when cholinesterase data in but one gender serves as the basis for an end point as important as the chronic RfD, e.g. carbofuran. (**Att 5**) Additional testing in animal models should be pursued to quantitate the magnitude of the gender specific disparity, while in the interim employing an additional 10-fold modifying factor since no data exists for women, or girls in particular.

II - "Process"

1) *Absence of Acknowledgment of External Peer Review and Consideration of Literature References in FQPA Safety Factor Committee Report of August 6, 1998.*

The December 17, 1997 HIARC report removed the FQPA 10X safety factor for the protection of infants and children, and concluded among other things the Developmental Neurotoxicity Study would not be required for malathion. In my view, the rationale for both of these decisions as presented in the 1997 HIARC report (**Att 2**) is inadequate. Furthermore, there is little evidence the subsequent **August 6, 1998 report of the FQPA Safety Factor Committee** (**actually a joint report of the HIARC and FQPA Safety Factor Committees**) (t-drive available), also recommending the safety factor's removal, contributed any more definitive evidence. It appears the latter committee simply endorsed the recommendation provided in the **July 7, 1998 HIARC "Hazard Assessment of the Organophosphates"** (t-drive available). This is particularly troubling because this July 7 HIARC report deleted the malathion literature reference portions that had appeared in the December 17, 1997 HIARC report on malathion. Thus, there is no mention of literature references in the August 6, 1998 FQPA Safety Factor Committee's evaluation of malathion with respect to its decisions on the status of *either* the 10X safety factor or the need for a Developmental Neurotoxicity Study. Also absent from these July 7 and August 6 reports is any reference to the External Peer Review on malathion received in June 1998 (**Att 1**) and reviewed July 21 (**Att 12**), where questions as to the status of the FQPA 10X safety factor and the need for a Developmental Neurotoxicity or other behavioral effects testing requirements were among those under consideration. The point is, the External Peer Review for malathion was OPP/HED approved, and while External Peer Reviews are important to the deliberative process, in this case the External Peer Review finds no mention in the FQPA Safety Factor Committee Report. *In my view, removal of the literature review component from the original December 17, 1997 HIARC report, and lack of acknowledgment of the External Peer Review in the FQPA Safety Factor Committee report of August 6, 1998 in the consideration of* ***both*** *the 10X safety factor and status of requirement of the Developmental Neurotoxicity study represent procedural anomalies.*

2) *Concerning the question of susceptibility, I advised HIARC of certain published works providing evidence of increased susceptibility of younger animals to the effects of malathion.*

*These appear in reputable sources, certain ones appearing even in HED's one-liners. [**Att 17 and 18** (p. 154)]. However, there has been no acknowledgment of this information. It appears as though the information has been ignored by HIARC and the FQPA Safety Factor Committee in the decision to remove the Congressionally imposed 10X safety factor for the protection of infants and children.*

3) *Concerning the susceptibility issue under FQPA, there is evidence of increased pup susceptibility in the Guideline Reproduction Study. The evidence of increased susceptibility of younger animals has been discounted by HIARC on the basis of rationale that has been questioned. On the one hand, HIARC proclaims as scientific fact that which has not been determined scientifically, namely that malathion ingested in mother's milk establishes a greater intake of malathion in pups on a body weight basis than that ingested by dams. Yet in my witness, malathion has not been shown to be present in dam's milk, let alone any quantitative analysis that could establish pup intake that might explain away evidence of enhanced pup susceptibility. This fallacious argument, absent data, on so critical an issue as that of the retention/removal of the FQPA 10X safety factor, should be questioned as a procedural or "process" issue. (**Att 8**; **Att 18**, p. 148) On the other hand, HIARC has ignored my request for external re-review of the DER and Study Report of the Reproduction Study to address the study author's conclusion that dams were not affected at any dose level in the study. (**Att 15**; **Att 18**, p. 148)*

4) *HIARC referral of External Peer Review Panel report to the FQPA Safety Factor Committee?*

In HIARC's final report of December 22, 1998, the committee disowns any responsibility to address the safety factor issue, but defers to the earlier decision of the FQPA Safety Factor Committee. (**Swetz99**, p. 1) So to the extent this obtains, did the HIARC ever refer the External Peer Review Panelists' reports to the FQPA committee for consideration. Either HIARC or the FQPA Safety Factor Committee should respond to the External Peer Review on the FQPA Safety Factor issue.

5) *In addition to eight major topics or sets of questions I submitted for External Peer Review, which the Panelists responded to, there were preliminary questions posed by HED's External Peer Review Coordinator to which the Panelists also responded. These questions pertained to the acceptability of the various DERs, whether critical effects were chosen in the various studies and whether the data base is complete. These are important questions pertaining to the assessment of the reliability of the data base under FQPA. Even though I expressed my concerns to the HIARC Chairman that the HIARC discussions not be restricted to review of the eight topics. (**Att 16 and 18**) I find no evidence HIARC reviewed the Panelists' responses to the coordinator's questions.*

6) *Since it was well known within OPP/HED that malathion issues were under External Peer Review, at the very least shouldn't the FQPA Safety Factor Committee have held in abeyance its consideration of this issue until availed of the External Peer Reviewers' responses?*

7) *I question the lack of invitation extended to persons such as myself, i.e. those who are very involved in the toxicology of a particular agent, to be present when the FQPA Safety Factor Committee considers the agent, as was true in the case of malathion. Due process should instruct otherwise.*

8) *Presumably during the deliberative process and prior to issuance of a final report, results of HIARC meetings are confidential. Yet, during the August 1998 HIARC meetings on malathion, a representative of the registrant was advised on August 18-19 that the HIARC elected to impose an additional 3-fold modifying factor on the chronic RfD, and was referred to an individual participating in the HIARC meetings, while deliberations of the committee were not complete until August 27, and the final report not written until December 22, 1998.*

9) *On August 18, the HIARC elected to impose an additional 3-fold modifying factor to the chronic RfD. The committee as convened on August 20 was advised by one of the participants that "management" was not pleased with the added modifying factor, indicating that it should be removed. The factor was removed on August 20, though I am unable to say to what extent the decision was driven by the management's intrusion into the deliberative process as described. It is because of activities such as this that I became more resolved that external reviews are necessary.*

10) *Given the disagreements that resulted in the External Peer Review, I do not accepted as proper or objective a role for the HIARC in ruling on the merits of the Panelists' comments, i.e. the decisions of the External Peer Review should either be accepted and implemented, or judgement on the merits rendered by yet another body of outside experts.*

11) *In my witness, at the August 1998 HIARC meetings, too little time was allocated for proper discussion of the many malathion issues. Stated differently, too many issues were slated for the designated time frame. This resulted in superficial presentations by designated "experts" on each topic. The experts presented little or no evidence to substantiate their conclusions, and most members of the HIARC accepted in unqualified manner the pronouncements of the designated experts. The "process" issue in this instance is that agenda for these meetings need to be established well before the meetings, with input from participants, there should be time for follow-up as needed, and the right of full debate secured.*

Attachments

Identification of CD icons cited: The 18 "Attachments" on the following list are the same as those appearing under the list of *Attachments* to the December 22, 1998 report of the Hazard Identification Assessment Review Committee (HIARC) (p. 18) and, hence, are retrievable electronically from that HIARC report.

057701ha.002:	December 22, 1998 HIARC report, HED Doc. No. 013032
Attachment 1:	Evaluations by the External Peer Review Members
Attachment 2:	December 17, 1997 HIARC report
Attachment 3:	November 10, 1997 memo to Clark Swentzel
Attachment 4:	November 20, 1997 memo to Clark Swentzel
Attachment 5:	November 25, 1997 memo to Clark Swentzel
Attachment 6:	December 17, 1997
Attachment 7:	January 15, 1998 memo to Clark Swentzel
Attachment 8:	February 10, 1998 memo to Clark Swentzel
Attachment 9:	March 10, 1998 memo to Jess Rowland
Attachment 10:	March 16, 1998 memo to Jess Rowland
Attachment 11:	March 20, 1998 memo to Clark Swentzel
Attachment 12:	July 27, 1998 memo to Clark Swentzel; appended: July 21, 1998 "Consolidation of External Peer Reviewer's Comments on Malathion Non-Cancer Issues" by B. Dementi.
Attachment 13:	July 29, 1998 memo to Clark Swentzel
Attachment 14:	August 3, 1998 memo to Clark Swentzel
Attachment 15:	August 10, 1998 memo to Clark Swentzel
Attachment 16:	August 17, 1998 memo to Clark Swentzel
Attachment 17:	September 24, 1998 memo to Clark Swentzel (conveys Mendoza, et al, date, not available electronically, but is available under MRID 45046301)
Attachment 18:	November 5, 1998 memo to Clark Swentzel
Swetz99:	January 29, 1999 memo to Clark Swentzel
Ehrich:	January 18, 2000 memo to Paula Deschamp conveying Ehrich, et al (1993), not available electronically. The publication is available under MRID 45045001.

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